IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kohl et al.

Serial No.: 045,799 (Continuation of SN 748,591)

Filed: April 28, 1987

For: DIALKOXYPYRIDINES, PROCESSES FOR THEIR PREPARATION, THEIR USE AND MEDICAMENTS CONTAINING THEM

Group Art Unit: 121

Examiner: Jane T. Fan

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

December 02, 1987

Sir:

DECLARATION UNDER RULE 132

I, KONRAD HEINTZE, declare and say:

1. THAT, I am a citizen of the Federal Republic of Germany, residing at Mühlengasse 14, D-7753 Allensbach, Federal Republic of Germany.

   THAT, from 1963 to 1968, I studied Medicine at the Universities of Berlin and Freiburg.

   THAT, I received the degree of Doctor of Medicine in 1969 and was admitted to practice on January 01, 1970.

THAT, I was Medicinal Assistant at the Marien-Hospital, Aachen from November, 1968 to August, 1969, and at the August-Victoria Hospital, Berlin from October, 1969 to February, 1970.

THAT, I worked as Assistant Professor at the Department of Pharmacology of the Rheinisch-Westfälische Technische Hochschule (University), Aachen from July 01, 1970 to May 19, 1976.

THAT, on May 19, 1976, I was given venia legendi (Associated Professor) in Pharmacology and Toxicology from Rheinisch-Westfälische Technische Hochschule, Aachen.

THAT, on November 10, 1976, I was awarded the diploma of "Facharzt für Pharmakologie" (medical expert in pharmacology) by the General Medical Council of Nordrhein-Westfalen.

THAT, from March 1978 to May 1979, I stayed in the United States of America and worked together with Professor Frizzell at the Department of Physiology, University of Pittsburgh, Pittsburgh.

THAT, on August 08, 1979, I was appointed a "Außerplanmäßiger Professor" (Section Head) by the Rheinisch-Westfälische Technische Hochschule, Aachen.

THAT, on October 01, 1982, I entered the Byk Gulden Lomberg Chemische Fabrik GmbH as head of the Pharmacology Department.

THAT, I am the author and coauthor of numerous scientific publications including those listed on the attachment hereto.

THAT, I am thoroughly familiar with evaluating chemical compounds for their protective action on the stomach and intestine of warm-blooded animals.

THAT, with regard to structure-activity relationship and stability problems, I am fully conversant with the class of compounds of substituted 2-(2-pyridylmethylsulfinyl)-benzimidazoles as described and claimed, for example, in U.S. patent application SN 045,799 and U.S. patents no. 4,555,518 and 4,560,693.

THAT, I have reviewed and I am well acquainted with Uwe Krüger's Declaration under Rule 132 of April 24, 1987, filed on April 28, 1987.

2. THAT, in order to comply with item 1 of the Official Action of September 01, 1987, the following comparative tests were performed in the laboratories of Byk Gulden Lomberg Chemische Fabrik GmbH under my supervision and direction:

Comparative Tests

Compounds

The following compounds of U.S. patent application SN 045,799 (A) and U.S. patents no. 4,555,518 (D) and 4,560,693 (E) listed in Table 1 have been investigated in the comparative tests:

Table 1

Compound No.	Origin	Name
4	D	5-Difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
5	A	5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
12	D	2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
14	A	2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
13	D	2-[(4-Methoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
15	A	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
17	D	2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole
18	A	2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole
20	D	5-Difluoromethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole

Table 1 Continuation

Compound No.	Origin	Name
21	A	5-Difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole
24	E	2,2-Difluoro-6-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
25	A	2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
29	E	6,6,7-Trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole
30	A	6,6,7-Trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole

The compound numbers listed above correspond to the compound numbers of Tables 1 and 2 in Uwe Krüger's Declaration of April 24, 1987.

Methods

The antiulcerogenic action and the inhibition of gastric secretion were tested on the so-called modified Shay rat: Rats (female, 180 to 200 g, 4 animals per cage on a high grid) which had been fasted for 24 hours were subjected to ulcer provocation by pylorus ligature (under diethyl ether anaesthesia) and oral administration of 100 mg/kg of acetylsalicylic acid. The substances to be tested were administered orally (10 ml/kg) 1 hour before the pylorus ligature. The wound was closed by means of Michel clamps. 4 hours thereafter, the animals were killed under ether anaesthesia by atlas dislocation, and the stomach was removed. The amount of the secreted gastric juice (volume) and its hydrochloric acid content (titration with sodium hydroxide solution) were determined. The stomach was opened longitudinally and fixed to a cork tile. The number and size (=diameter) of ulcers present were determined with a stereomicroscope with 10-fold magnification. The product of the degree of severity (according to the following rating scale) and the number of ulcers serves as the individual ulcer index.

Rating scale:		
no ulcers		0
ulcer diameters	0.1 - 1.4 mm	1
	1.5 - 2.4 mm	2
	2.5 - 3.4 mm	3
	3.5 - 4.4 mm	4
	4.5 - 5.4 mm	5
	> 5.5 mm	6

The reduction in the average ulcer index of each treated group compared with that of the control group (=100 %) serves as a measure of the antiulcerogenic effect. The ED_{50} designates the dose which reduces the average ulcer index and the gastric secretion by 50 % in the treated group compared with the control group.

The effect of a single dose on the ulcer index and the inhibition of HCl-secretion is characterized by the median of all possible ratios treatment/control [point estimator according to Hodges and Lehmann, M. Hollander and D.A. Wolfe: Nonparametric Statistical Methods, J. Wiley & Sons, New York (1973), pp. 75-78]. From this, the percent reduction or inhibition versus control is calculated as follows:
Percent reduction (inhibition) = 100 x (1-median of ratios).

The ED_{50} is calculated by means of logarithmic-linear regression (y = %inhibition, x = log dose); the 95%-confidence limits of the ED_{50} values are calculated by standard procedures [see e.g. K.A. Brownlee, Statistical Theory and Methodology in Science and Engineering, 2nd edition; Wiley, New York (1965), p. 348]. The differences in ED_{50} values is considered significant at the 5%-level if the 95%-confidence limits do not overlap.

Results

The effect of the compounds according to the invention and of the compounds of the closest prior art on the formation of gastric ulcers provoked by a pylorus ligature (4 hours, modified Shay rat) and oral administration of 100 mg/kg acetylsalicylic acid and on the inhibition of gastric secretion in rats during 4 hours is shown in the following Table 2:

Table 2

Antiulcerogenic action and inhibition of gastric acid secretion

Compounds of SN 045,799 (5, 14, 15, 18, 21, 25, 30) compared with compounds of USP 4,555,518 (4, 12, 13, 17, 20) and USP 4,560,693 (24, 29)

No	Dose (µmol/kg) orally	N	Protective action on the stomach (rat) reduction of ulcer index (%)	Sign.+ P	ED_{50} (with 95 % confidence limits) µmol/kg p.o.	Gastric acid secretion+ (rat) inhibition in % of HCl-secretion	Sign.+ P	ED_{50} (with 95 % confidence limits) µmol/kg p.o.
4	0.27	16	9	n.s.		8	n.s.	
	0.54	8	30	n.s.		34	n.s.	
	0.82	16	62	*	0.73 (0.35-1.12)	24	n.s.	1.03 (0.54-1.93)
	1.63	8	100	*		84	*	
	2.72	8	100	*		79	*	
5	0.078	16	14	n.s.		-12	n.s.	
	0.26	15	40	*		15	n.s.	
	0.78	16	47	*		14	n.s.	
	1.56	16	76	*		27	*	
	2.61	8	78	*	0.60 (0.15-1.30)	65	*	2.35 (1.04-4.38)
	3.91	8	87	*		64	*	
	5.22	8	100	*		82	*	
	7.82	8	100	*		74	*	
	15.65	8	100	*		84	*	
12	0.72	24	12	n.s.		26	*	
	0.96	24	66	*		37	*	
	1.44	16	80	*	0.93 (0.77-1.20)	52	*	1.53 (0.93-2.23)
	1.92	16	88	*		50	*	
	2.40	15	100	*		76	*	
14	0.23	16	23	*		8	n.s.	
	0.69	16	40	*		3	n.s.	
	2.31	16	72	*	1.08 (0.48-2.15)	41	*	2.83 (1.73-3.99)
	4.62	8	100	*		71	*	
	6.92	8	100	*		83	*	
13	0.72	16	29	n.s.		-8	n.s.	
	2.40	16	55	*	1.96 (0.79-6.18)	16	n.s.	6.13 (3.52-n.d.)
	7.19	8	88	*		57	*	
15	0.69	16	38	*		25	*	
	1.38	8	45	*		18	n.s.	
	2.31	8	68	*	1.41 (n.d.-8.77)	23	n.s.	9.88 (2.28-n.d.)
	6.92	8	74	*		37	*	
	13.85	8	100	*		66	*	
	23.08	7	100	*		81	*	
17	0.75	8	15	n.s.		-3	n.s.	
	1.50	8	53	*		42	*	
	2.00	7	100	*	1.48 (0.98-1.73)	71	*	1.50 (1.05-2.08)
	2.50	8	100	*		78	*	
	5.01	8	100	*		90	*	
	7.51	8	100	*		92	*	
18	0.3	8	17	n.s.		10	n.s.	
	1.0	16	38	*	1.40 (0.71-1.86)	5	n.s.	2.65 (2.40-2.92)
	2.0	16	66	*		19	*	
	3.0	8	100	*		68	*	

Table 2 Continuation

No	Dose (µmol/kg) orally	N	Protective action on the stomach (rat) reduction of ulcer index (%)	Sign.+ P	ED_{50} (with 95 % confidence limits) µmol/kg p.o.	Gastric acid secretion+ (rat) inhibition in % of HCl-secretion	Sign.+ P	ED_{50} (with 95 % confidence limits) µmol/kg p.o.
20	0.15	24	6	n.s.		11	n.s.	
	0.25	16	51	*		23	*	
	0.50	16	38	*		19	n.s.	
	0.75	16	73	*	0.45 (0.22-0.91)	28	*	1.31 (0.65-2.21)
	1.51	24	76	*		44	*	
	2.01	15	100	*		79	*	
	2.52	16	100	*		83	*	
	5.03	16	100	*		90	*	
21	0.24	8	2	n.s.		10	n.s.	
	0.73	16	34	*	1.21 (0.36-2.66)	1	n.s.	3.39 (2.08-4.84)
	2.42	15	71	*		37	*	
	7.26	16	100	*		88	*	
24	0.16	16	23	n.s.		-6	n.s.	
	0.26	16	42	*		3	n.s.	
	0.52	16	47	*		5	n.s.	
	0.79	16	67	*	0.50 (0.21-0.81)	29	*	1.29 (0.94-1.73)
	1.57	16	100	*		53	*	
	2.62	16	100	*		80	*	
	5.25	8	100	*		91	*	
25	0.25	8	11	n.s.		-5	n.s.	
	0.76	16	52	*	1.01 (0.28-2.04)	20	n.s.	4.50 (3.20-5.69)
	2.52	15	63	*		27	*	
	7.55	8	100	*		81	*	
29	0.73	16	38	*		24	n.s.	
	1.45	15	84	*	0.85 (0.70-1.14)	51	*	1.43 (0.85-2.06)
	2.42	16	100	*		74	*	
30	1.0	16	11	n.s.		2	n.s.	
	3.0	16	54	*	2.71 (1.52-3.99)	7	n.s.	6.96 (5.46-8.52)
	10.0	8	100	*		79	*	

No = Compound Number (according to the numbers in Uwe Krüger's Declaration of April 24, 1987)
N = Number of Animals
+) = Significance: n.s. = not significant; * = $p < 0.05$
++) = ED_{50} = dose which reduces the ulcer index and the HCl-secretion (sum of 4 hours) of the rat stomach by 50 % in the treated group compared with the control group
a.d. = not detectable

Discussion

The compounds tested in the comparative tests have been selected on account of the comments set forth under item 3 in the Official Action of September 01, 1987.

The data in Table 2 clearly indicate that in these comparative tests the compounds of SN 045,799 (compounds 5, 14, 15, 18, 21, 25 and 30) have a protective action on the stomach which, on the whole, is comparable to that of the compounds of USP 4,555,518 (compounds 4, 12, 13, 17 and 20) and USP 4,560,693 (compounds 24 and 29): Compounds 14 and 18 (as compared with compounds 12 and 17) can be regarded as being equally potent, compounds 5 and 15 (as compared with compounds 4 and 13) are slightly more potent, compounds 21 and 25 (as compared with compounds 20 and 24) are slightly less potent in these tests. Solely the smaller potency of compound 30 (with a factor of about 3 as compared with compound 29) differs to some extent from the general picture.

In view of the fact that (apart from the pair 29/30) the differences in the protective action on the stomach observed in the comparative tests compiled in Table 2 are statistically not significant (overlap within the 95 % confidence limits), it can be said that the compounds of SN 045,799, USP 4,555,518 and USP 4,560,693 are approximately equal in potency. Thus, the reduced reactivity at a pH of 5 as compared with the compounds of USP 4,555,518 and USP 4,560,603 which has been substantiated in Uwe Krüger's Declaration of April 24, 1987, proves to be an outstanding and advantageous property of the compounds of SN 045,799 which - in view of the comparable potency - makes itself fully felt.

3. The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance, Federal Republic of Germany,
this 4 day of December, 1987.

K. Heintze

Prof. Dr. Konrad Heintze

Referreed Publications

1. HEINTZE, K.:
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11. HEINTZE, K. and K.-U. PETERSEN:
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1. HEINTZE, K., O. HEIDENREICH:
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